Claims 1-16, 17, 23, 24, 33, 35, 38, and 39 have been amended herein to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Support for these amendments is found in the specification as filed and as more fully set forth below. Thus, no new matter has been added by way of these amendments.

Objection to the Specification

The disclosure stands objected to because the abbreviations "RANTES" and "MIP" are not defined. In the Examiner's opinion, appropriate correction is required.

While these terms are well-known in the art and are provided in the references cited in the specification as filed, Applicants, in a good faith effort to expedite prosecution of this application, have amended the specification to recite the full terms for these abbreviations at the site of first occurrence of these terms. More specifically, pursuant to 37 CFR § 1.121(b)(1), Applicants have replaced the paragraph on page 3, lines 24 to 27, with a replacement paragraph wherein the terms are now spelled out. A clean version of the paragraph without markings is provided above and a "marked-up" version of the replacement paragraph is provided herewith on a separate page, indicating all the amendments made thereto relative to the original paragraph.

Objections to Claims 13, 28, 32, 33, and 35

Claims 13, 28, 32, 33, and 35 stand objected to because in the Examiner's view, these claims recite various informalities. Since claims 28 and 32 have been cancelled herein without prejudice, the objections relating to these claims have been rendered moot and are not addressed herein.

Claims 13 and 33 have been amended to spell out the acronyms used in the first instance in these claims. Claim 35 has been amended to correct a grammatical error pointed out by the Examiner, *i.e.*, "a" has been changed to "an". These amendments are supported by the specification as filed and add no new matter.

Provisional Rejection of Claims 25-28 and 30-32 under 35 U.S.C. §101, for Statutory Double Patenting

Claims 25-28 and 30-32 stand provisionally rejected, under 35 U.S.C. §101, as claiming the same invention as claims 43, 47-50 and 52-54 of co-pending Application No.

09/322,275 (Office Action at page 3). Applicants respectfully point out that as noted by the Examiner on page 4 of the Office Action, the copending application is numbered Ser. No. 09/332,275. Thus, for purposes of this rejection, Applicants assume that the copending application referenced by the Examiner is No. 09/332,275, filed on June 11, 1999, as stated by the Examiner on page 4 of the instant Office Action.

Applicants, while not necessarily agreeing with the Examiner's position, in a good faith effort to expedite prosecution of this application, have cancelled claims 25-28 and 30-32 of the instant application herein. Applicants submit that the cancellation of claims 25-28 and 30-32 renders the provisional statutory double patenting rejection of these claim, under 35 U.S.C. §101, moot. Therefore, Applicants respectfully request that the statutory double patenting rejection be reconsidered and withdrawn.

Provisional Rejection of Claims 1, 2, 5-16, 18-22, 25-35, and 38, Under Judicially Created Non-Statutory Obviousness-Type Double Patenting Doctrine

Claims 1, 2, 5-16, 18-22, 25-35, and 38, stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 6, 8-16, 18-20, 23, 26, 28-36, 38-42, 44-46, and 51 of copending Application No. 09/322,275 (Office Action at page 3). As pointed out previously elsewhere herein, for purposes of this rejection, Applicants assume that the Examiner was referring to U.S. Patent Application No. 09/332,275, which is copending with the instant application, as pointed out by the Examiner on page 4 of the instant Office Action.

Substantively, in the Examiner's view, although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the generic claims of copending Application No. 09/332,275 render the species claims in the instant application obvious. The Examiner also asserts that the claims in copending Application No. 09/332,275, while broader than the instant claims, specifically recite the species claimed herein, thus rendering them obvious.

Preliminarily, Applicants have cancelled claims 25-28 and 30-32 herein and, therefore, the provisional obviousness-type double patenting rejection is now moot with respect to these claims.

Applicants, while not necessarily agreeing with the Examiner's position, in a good faith effort to expedite prosecution of this application, agree to file a Terminal Disclaimer in the co-pending application upon notice that claims 1, 2, 5-16, 18-22, 29, 33-35, and 38, in this application contain allowable subject matter.

Accordingly, since claims 25-28 and 30-32 have been cancelled herein and since Applicants have agreed to file a Terminal Disclaimer in copending Application No. 09/332,275, the rejection of claims 1, 2, 5-16, 18-22, 29, 33-35, and 38, under the judicially created obviousness double patenting doctrine is now moot and this provisional rejection should be reconsidered and withdrawn.

Rejection of claims 1-39 pursuant to 35 U.S.C. § 112, first paragraph

Claims 1-39 stand rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's opinion, the claims are not enabled. More specifically, in the Examiner's view, the claims are broad and encompass gene therapy and, while the relative skill of those in the art of gene therapy is high, the area is unpredictable and *in vivo* and *ex vivo* gene therapy methods would require undue experimentation. The Examiner, purportedly applying the factors set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), cites the following references in support of the rejection: Verma and Somia (1997, Nature 389:239-242); and Fox (2000, ASM News 66:1-3). Applicants respectfully submit that claims 1-24, 29, and 33-39 (claims 25-28 and 30-32 having been cancelled herein) are enabled as more fully set forth below.

Preliminarily, claims 25-28 and 30-32 have been cancelled herein thereby rendering the rejection moot as to these claims.

Applicants respectfully submit that the claimed cell and gene therapy methods are enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph, and traverse the rejections of claims 1-39 under 35 U.S.C. § 112, first paragraph, for the reasons set forth below.

It is well-settled that an Applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. MPEP §2164.02 (citing *Gould v Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*in*

re Borkowski, 422 F.2d 904, 908 (C.C.P.A. 1970), and "representative samples are not required by the statute and are not an end in themselves" *(in re Robins*, 429 F.2d 452, 456-457, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *in re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled in the art and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Preliminarily, Applicants do not understand the Examiner's assertion in support of the rejection that claims 1, 17, 23, 24, and 35 are broad, as there is no *per se* prohibition against broad claims. Further, Applicants respectfully submit that, contrary to the Examiner's assertions, the disclosure in the specification as filed amply supports, *inter alia*, methods of inhibiting phenotypic expression of a chemokine receptor in a cell comprising blocking cell surface expression of said chemokine receptor, a method of inhibiting HIV infection of a cell by knocking out phenotypic expression of an HIV co-receptor, and an expression vector comprising a promoter and fusion of an intracellular retention signal sequence coding region to a chemokine encoding gene with additional expression of a chemokine using an IRES. The specification as filed amply supports such methods because even though no working example is required under current law, there has been extensive reduction to practice in this instance. Indeed, as more fully set forth below, all of the afore-mentioned subject matter has been reduced to practice by Applicants as demonstrated by the disclosure provided in the specification, as filed.

Specifically, the specification as filed demonstrates that Applicants have fully enabled the use of intracellularly retained chemokines or cytokines to prevent transport of receptors to the cell surface and inhibition of HIV infection of cells comprising the vectors of the invention, as well as use of secreted chemokines to competitively inhibit HIV-1 from binding

with a co-receptor on a cell, and, even more remarkably, to inhibit infection of the cell and to inhibit cell-to-cell spread of the virus by inhibiting syncytia formation.

More specifically, for instance, the disclosure teaches the specific targeting of chemokines to specific intracellular locations, including specific examples using RANTES, MIP-1α, and SDF-1 such that they become "intrakines" as that term is used, defined, and exemplified by the specification as filed (*see, e.g.*, Figures 1-4).

Further, the invention enables a method in which sequences encoding a chemokine of choice are linked to intracellular targeting sequences and can be used to phenotypically knock out the cognate receptor for the chemokine. More specifically, the specification demonstrates inhibition of CCR5 and CXC4 receptor expression at the cell surface (Figure 2, Figure 3A, Figure 3B, Figure 3C, Figure 3D, Figure 4). Such inhibition, or phenotypic knocking out, in turn, inhibits infection of cells by HIV-1 (Figure 2- Figure 4), since the virus requires the presence of these receptors at the cell surface.

Furthermore, the disclosure demonstrates additional reduction to practice of methods for preventing virus infection and discloses that human peripheral blood lymphocytes (PBLs) transduced with the chemokines RANTES or MIP1α are resistant to Mϕ-tropic HIV-1 infection (see Figure 2 and page 42, lines 5-25).

Thus, the specification as filed demonstrates reduction to practice of methods of phenotypically knocking out expression of chemokine receptors at the cell surface and inhibition of processes mediated by such receptors being present on the cell, including, but not limited to, virus infection of the cell.

The specification also demonstrates reduction to practice of methods of treating an HIV infection even after initial infection. That is, the data disclosed in the specification as filed demonstrate that syncytium formation induced by HIV is inhibited by transduction with intrakines, which is an example of treatment in that further spread of the virus is inhibited (*see, e.g.*, Figure 3E). The data disclosed in the specification as filed further demonstrate the use of bicistronic vectors where expression of a chemokine fused with a retention sequence and a secreted chemokine expressed from an internal ribosomal entry site (IRES) inhibited virus infection of cells and detectably knocked out phenotypic expression of the chemokine receptor at the cell surface. Thus, the specification as filed demonstrates extensive reduction to practice that

clearly enables the claims under 35 U.S.C. §112, first paragraph, which does not even require a single working embodiment.

Additionally, the data disclosed in the specification as filed, *e.g.*, at pages 7 and 8, demonstrate reduction to practice of methods of cell therapy using cells resistant to virus infection. That is, the data demonstrate that cells transduced with the vectors of the invention are resistant to virus infection. Therefore, cells obtained from a patient can be transduced and reintroduced into the patient thereby providing infection-resistant cells to the patient. Further, the invention discloses detailed methods for gene delivery and for therapy at pages 31-34 of the specification. Applicants assert that these disclosures provide ample guidance to one skilled in the art of treating an HIV infection and no undue experimentation would be required to practice the methods of the invention.

In addition, the chemokine stromal cell-derived factor-1 (SDF), a biological ligand for the receptor CXR4, is shown herein to be amenable to being targeted to the lumenal endoplasmic reticulum (ER) of lymphocytes (Figure 4A). Furthermore, the intracellular-retained SDF intrakine bound with newly synthesized CXR4 receptor and prevented its transport to the cell surface, thus, clearly enabling a method of blocking chemokine receptor cell surface expression. Moreover, these genetically modified lymphocytes without the co-receptor on the cell surface were found to be resistant to T-tropic HIV-1 infection (Figure 4A and Figure 4B; see page 43, line 2 to page 44, line 2; see also page 46, lines 3-23), further reducing to practice methods of inhibiting virus infection using intrakines, which methods are also enabled by the disclosure provided in the specification as filed.

The specification, at pages 7 through 38, set forth, in great detail, techniques and assays useful for practice of the present invention commensurate with the scope of the claims. The data disclosed in the specification as filed demonstrate that Applicants' invention relating to intrakines successfully targets a cellular receptor and therefore helps to overcome a major problem facing anti-HIV therapy, *i.e.*, frequent mutation of the virus, which results in virus resistance to vaccination. Contrary to the Examiner's assertion, the present invention represents a vast improvement over prior art vaccination methods since Applicants' methods exploit the virus' dependence on host cell receptors and, unlike prior art vaccination strategies, does not rely on immune recognition of virus components; indeed, Applicants' methods do not rely on immune recognition at all. Thus, the teachings of this invention do not relate to vaccination, as

urged by the Examiner at page 5 of the Office Action. Indeed, instead of reading on vaccination as stated by the Examiner, the methods of the invention overcome prior art obstacles of vaccination by using a novel method of preventing virus infection of cells.

In addition to extensive reduction to practice with regard to inhibition of HIV relating to cytokines and receptors on pages 7-11, the specification as filed provides extensive reduction to practice, teachings, and the like, amply enabling methods of making and using intrakine-encoding polynucleotides (specification at pages 11-16), knockout strategies (*id.* at pages 16-21), expression vectors (*id.* at pages 21-30), other viral vectors as expression constructs (*id.* at pages 30-31), methods for gene delivery (*id.* at pages 31-34), and therapeutic compositions (*id.* at pages 34-38).

Furthermore, Applicants respectfully submit that the literature cited by the Examiner to demonstrate that the art was unpredictable does not support the enablement rejection. That is, Verma and Somia (1997, Nature 389:239-242), a review article relating to gene therapy cited by the Examiner in support of this rejection, while pointing out the various difficulties associated with gene therapy, and numerous solutions thereto, demonstrated continued expression of an exogenous nucleic acid encoding Factor IX at high levels for the life of a mouse, *i.e.*, two years (see page 240, middle column), and therapeutic expression of Factor IX in mice for over 6 months using adeno-associated viral vectors (AAV). Therefore, Verma clearly demonstrates the high level of skill in the art where the pitfalls of gene therapy were known and that alternatives were also known as of September 1997. Thus, far from indicating that gene therapy cannot work, Verma demonstrates that gene therapy can work.

The Examiner also cites Fox (2000, ASM News 66:1-3) as an example of the unpredictability of the art. That is, Fox is apparently a non-peer reviewed news report relating to gene therapy clinical trials. Applicants respectfully submit that Fox does not support the enablement rejection. Although Fox notes a participant in a phase I gene therapy clinical trial died raising concerns regarding gene therapy, it also pointed out the extensive amount of gene therapy experimentation that had occurred but did not result in death. For example, at page 2, lines 32-40, Fox highlights the fact that the adenovirus vector which was being used in the patient who died, which had been developed by James Wilson of the University of Pennsylvania, had been tested extensively in several kinds of mice and primates. However, even at high

concentrations of the vector only some animals developed complications and only several animals died.

In addition, Fox notes that at the time, about 20 other individuals had been treated with the same vector. While several of the patients developed adverse symptoms, they were moderate. The news article also revealed some data suggesting that the patient who died had a parvovirus infection. Fox also notes that the University of Pennsylvania clinical trial was only one of several hundred gene transfer and gene therapy clinical procedures underway at the time. This reveals that gene therapy and associated techniques, even when viewed only with respect to work performed in humans, has been used extensively with only rare critical setbacks. When Fox and Verma are taken together and critically examined against a backdrop of what they show to be a high level of skill in the art, it can be seen that one of skill in the art would appreciate where the pitfalls of gene therapy lie and also the alternatives that were known in the art. Thus, Fox does not support an enablement rejection based on the premise that the art is unpredictable.

Moreover, Applicants have reduced to practice the phenotypic knock out of several chemokine receptors using various intrakines in a wide variety of cell types. Further, Applicants, using the intrakines of the invention, have inhibited virus infection of cells and horizontal infection of cells as demonstrated by inhibition of syncytia formation and have rendered a variety of cells resistant to virus infection. Given the extensive reduction to practice, the Examiner cannot, under the guise of an enablement rejection, issue a 35 U.S.C. §101, lack of utility rejection as she is apparently attempting to do by asserting that the only disclosed use is gene therapy which is not enabled. This is a circular argument where, as here, Applicants have transduced cells with novel vectors, and inhibited virus infection as exemplified by extensive reduction to practice. For instance, PBLs and immortal lymphocyte cells were rendered resistant to virus infection, demonstrating that an *ex vivo* approach can be used to treat a virus infection. This level of reduction to practice is well beyond that required for purposes of enablement under 35 U.S.C. §112, first paragraph, and the rejection based on lack of enablement should be reconsidered and withdrawn.

Further, at page 6 of the Office Action, the Examiner asserts that the specification discloses specific cell surface receptors to target in the case of HIV infection, but that it does not disclose specific chemokine receptors and their binding ligands to target in other diseases and

that the specification discloses no specific therapeutic molecules and diseases to which the claimed vectors and methods can be applied.

Applicants assert that the specification as filed does disclose other diseases (i.e., ARC at page 2, lines 17-19) and that specific chemokine receptors and their ligands are known to those of skill in the art. Furthermore, based on the teachings of this invention, one of skill in the art would be able to apply the invention to other diseases, including diseases not named in the invention that are commonly known to those of skill in the art. As discussed above, an applicant need not have actually reduced an invention to practice in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. MPEP §2164.02 (citing *Gould v Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (in re Borkowski, 422 F.2d 904, 908 (C.C.P.A. 1970), and "representative samples are not required by the statute and are not an end in themselves" (*in re Robins*, 429 F.2d 452, 456-457, 166 USPQ 552, 555 (CCPA 1970)).

There is no requirement under the current law of enablement that each embodiment be reduced to practice. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991), made clear that generic claims are not precluded by 35 U.S.C. §112, first paragraph, and that enablement does not require working examples for each species encompassed by a claim. *Accord in re Robbins*, 166 USPQ 552 (CCPA 1970).

Applicants have disclosed sufficient data and background to support claims reciting the use of chemokine receptors and their binding ligands to target other diseases. The results demonstrated in Figures 1-4B illustrate the general use and efficacy of intrakines in blocking polypeptide receptor transport to the cell surface. In addition, the use and administration of polynucleotides encoding such chemokines are described in detail from page 7 to page 50.

It is clear, that where, as Applicants have demonstrated for the first time a method of treatment by inhibiting or knocking out phenotypic expression of chemokine receptors, defined according to specific parameters, and where the art routinely screens for such treatment using numerous assays to assess that the method possesses those characteristics, which assays are known in the art and/or disclosed in the specification, experimentation to identify such agents and methods is not undue. For Example, at page 6, line 20 to page 7, line 3 of the Office Action

the Examiner interprets a statement in the application to mean that intrakine expression levels need not be high to achieve a therapeutic effect and in fact asserts that the statement is purely speculative. Applicants traverse the rejection for several reasons. First, the statement in question at page 8, lines 3-5 of the application was "CCR5 expression in human lymphocytes is very low (i.e., it cannot be detected in radiolabeling), and therefore, expression levels of intrakines achievable by currently used expression vectors are expected to be sufficient to inactivate CCR5." This statement merely suggests that currently available expression vectors should be adequate to achieve an effect, and this statement is in fact based on that which in known in the art and the fact that Figures 3A, 3B, 3C, 3D, and 3E demonstrate both physical and functional inhibition of CCR5 demonstrating the successful reduction to practice of Applicants' vectors and methods of using the same. Second, regardless of the what the levels of CCR5 are in the cells used, currently available expression vectors were indeed used to block CCR5 expression and treat HIV infection, as measured by formation of syncytia. Furthermore, Applicants respectfully submit that the reference to *In re Wands* (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)) to support the enablement rejection, in fact, does not support the rejection.

In the landmark enablement case of in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where, as here, the art typically makes and screens expression vectors to identify those encoding a protein which is expressed, more specifically, a chemokine, having the desired activity and/or properties, *e.g.*, the chemokine binds intracellularly to a chemokine receptor and inhibits receptor transport to the cell surface, one skilled in the art would not require undue experimentation to produce expression vectors encoding proteins having the desired biological function. Thus, where one skilled in the art routinely screens potentially useful expression vectors and expressed peptides, once the desired characteristics of such expression vectors are disclosed, where numerous working examples are provided demonstrating production and reduction to practice of numerous vectors, and where assays exist for assessing that a test expression vector or peptide has the characteristics, doing so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*.

In *In re Angstadt*, 190 USPQ 214 (CCPA 1976), the court addressed the level of experimentation in an unpredictable art, *i.e.*, the chemical arts, where the claimed invention involved a method of catalytically producing hydroperoxides where the specification admitted that not all disclosed complexes produced the hydroperoxides. The *Angstadt* Court, holding that the invention as claimed was enabled, reasoned:

> We note that many chemical processes, and catalytic processes particularly, are unpredictable. . . .
>
> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

In re Angstadt, 190 USPQ at 218 (emphasis added) (citations omitted).

Similarly, in *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981), the court noted the public policy reasons mitigating against imposing a requirement that each compound be tested before a generic species claim is allowed:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public.

Thus, where methods for assessing whether an expression vector encodes a protein having the utility of the claimed therapeutic agent, *e.g.*, a chemokine fused with an intracellular retention sequence wherein the intrakine has the ability to block intracellular transport of cell surface receptors, are well-known in the art and/or disclosed in the specification, where specific requirements for such expression vectors and intrakines are disclosed, and where the art routinely screens expression vectors and expressed peptides to identify those with a desired property/activity, it would not be undue experimentation to screen expression vectors for those encoding a peptide having the disclosed utility where the art typically engages in such screening. Further, the present invention discloses multiple examples of the use of expression vectors encoding different chemokines to block surface expression of various chemokine receptors and to block HIV infection, in various cell types (see Figures 1-4B). In addition, based on this extensive disclosure, one of skill in the art would be able to use the teachings to treat infected cells as well.

More recently, in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989), the Board reversed the Examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, with regard to an application involving admittedly "innumerable" muteins comprising a non-essential cysteine which exhibit biological activity after modification to substitute the cysteine. In reversing the Examiner, the *Mark* Court stated:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [an applicant]'s declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the claimed

> invention for a given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907. Therefore, where one skilled in the art routinely assays the compounds (*e.g.*, expression vectors encoding chemokines) for the asserted utility (*e.g.*, binding intracellularly with chemokine receptors, and thereby inhibiting chemokine receptor transport to the cell surface, resulting in treating or inhibiting HIV infection), it is not undue experimentation for them to do so.

For example, Applicants respectfully submit that the disclosure teaches throughout that a phenotypic knockout cell expressing a receptor binding polypeptide fused to an intracellular retention signal sequence can bind to one of the receptors as is recited in claim 24. In fact claim 23, from which 24 depends, claims a phenotypic knockout for HIV co-receptors. Phenotypic knockout is defined and used throughout the specification, including page 4, lines 12-18 and Figure 1. Also, the chemokines, intrakines, and co-receptors claimed in claim 24 are fully disclosed throughout the specification. Chemokines and their receptors are described in detail in the sections entitled "Chemokine Receptors," pages 9-10, and "Intrakine Polypeptides," pages 10-11, and in Examples 1-8. Furthermore, claims 23 and 24 have been amended herein to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

Further, one skilled in the art, armed with the teachings and extensive reduction to practice provided in the specification as filed, would have been able, without undue experimentation, to use the methods of the invention to modulate expression of a wide plethora of cell surface proteins for which receptor/ligand partners were known. Thus, following the teachings provided in the specification as filed, the skilled artisan who routinely used recombinant technology would have been able to produce and identify intrakines to inhibit expression of any receptor molecule on the surface of a cell without undue experimentation. That is, for any known chemokine/chemokine receptor combination, the skilled artisan would have been able to produce the intracellularly retained intrakine and to identify such constructs

that inhibited cell surface expression of the cognate receptor molecule as exemplified and reduced to practice in the specification as filed, and using methods and assays well-known in the art.

Applicants respectfully submit that undue experimentation would not have been required to practice the present invention commensurate with the scope of the claims to other diseases or conditions where phenotypic knock out of a surface receptor would have been understood by the skilled artisan to be useful. This is especially true where, as would be appreciated by one skilled in the art, chemokines are a family of structurally related peptides and where chemokine receptors are members of the 7 transmembrane G-protein coupled receptor family of cell receptors which are highly conserved and well characterized (*see, e.g.*, specification at page 10, lines 3 to 28). Thus, Applicants submit that the present invention is enabled not only with respect to the chemokines and cognate chemokine receptors exemplified and/or reduced to practice in the specification as filed. Rather, the invention encompasses and enables use of intrakines to any chemokine/chemokine receptor binding pair since no undue experimentation would have been required of the skilled artisan armed with the teachings provided in the specification as filed to use the methods of the invention with regard to any such chemokine/receptor binding pair.

In sum, for the reasons stated above, Applicants respectfully submit that claims 1-24, 29, and 33-39, are enabled by the disclosure provided in the specification as filed for purposes of 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully request that the rejection of these claims be reconsidered and withdrawn.

Rejection of claims 8-16, 19, and 23-39, pursuant to 35 U.S.C. § 112, second paragraph

Claims 8-16, 19, and 23-39 (now 8-16, 19, 23-24, 29, and 33-39, since claims 25-28 and 30-32 have been cancelled herein), stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully submit that the claims as amended are not indefinite as more fully set forth below.

Preliminarily, claims 25-28 and 30-32, have been cancelled herein without prejudice, rendering this rejection moot as to those claims.

Claims 8-12 and 14 stand rejected for reciting "the" instead of "a" with regard to various chemokine receptors there being, according to the Examiner, insufficient antecedent

basis for this limitation. Applicants, in a good faith effort to expedite prosecution of this application, have amended claims 8-12 and 14 to recite "a". No new matter has been added by way of these amendments which merely place the claims in proper form in the Examiner's view. Applicants respectfully submit that claims 8-12 and 14, as amended, are not indefinite in any way, and this rejection should be reconsidered and withdrawn.

Claim 13 stands rejected because, in the Examiner's view, it is indefinite for reciting the term "the encoded chemokine." Applicants, while not necessarily agreeing with the Examiner's reasoning, have, in a good faith effort to expedite prosecution of this application, amended claim 13 to recite that the chemokine referenced is a secreted chemokine. Support for this amendment is found throughout the specification as filed, commencing at page 3, line 6, disclosing, *inter alia*, a bicistronic molecule comprising a nucleic acid encoding an intrakine and further comprising a secreted chemokine. Thus, no new matter has been added by way of this amendment. Applicants respectfully submit that claim 13, as amended, is not indefinite in any way, and this rejection should be reconsidered and withdrawn.

Claim 15 stands rejected as being indefinite for reciting the term "the encoded chemokine". Applicants have amended claim 15 to recite that this chemokine is the secreted chemokine. Support for this amendment is found throughout the specification as filed, commencing at page 3, line 11, which discloses that the secreted chemokine can be mutated and that the mutation comprises deletion of at least one amino acid from the N-terminus of the chemokine. Thus, no new matter has been added by way of this amendment. Applicants respectfully submit that claim 15, as amended, is not indefinite in any way, and this rejection should be reconsidered and withdrawn.

The Examiner has rejected claim 16 because the claim is indefinite for reciting the term "the expressed protein," because in his opinion, there is insufficient antecedent basis for this limitation. Applicants have amended claim 16 to recite "a protein expressed from the single intrakine transcript" in place of the term "the expressed protein." Support for this amendment is filed throughout the specification as filed, commencing at page 3, line 3. More specifically, the specification discloses that the protein, *i.e.*, an intrakine, expressed from the single transcript comprising an intracellular retention sequence and a nucleic acid encoding a chemokine, is retained in an intracellular compartment where it binds with a cognate receptor thereby preventing expression of the receptor on the cell surface. Therefore, no new matter has been

added by way of this amendment. Applicants respectfully submit that claim 16, as amended, is not indefinite in any way, and this rejection should be reconsidered and withdrawn.

Claim 19 stands rejected because the Examiner contends the claim is vague for reciting the term "a chemokine analog." The Examiner asserts that the term is not a term of art and that it is not defined in the specification. Applicants respectfully submit that the term chemokine analog is defined in the specification as filed and is even exemplified therein. For instance, the specification at page 3, lines 11-16, discloses that the chemokine of the invention encompasses mutated forms of a chemokine that maintain receptor binding but lack biological activity. That is, the analog can bind with the receptor but does not mediate the biological activity/effect on cellular processes that binding of the receptor with its cognate ligand typically does. The specification continues noting "such a chemokine analog in which eight amino acids are deleted from the N-terminus is described by Arenzana-Seladedos et al. In the practice of the invention, one or more of the N-terminal amino acids may be deleted to obtain such a chemokine analog." Specification at page 3, lines 13-16 (emphasis added) (citation omitted). Also, the specification makes clear, by example, that "a chemokine analog, such as a chemokine with an N-terminal deletion of up to eight amino acids" is included in the invention. Specification at page 4, lines 3-5.

Thus, the specification as filed makes it clear that a chemokine analog is a mutated form of a chemokine that maintains receptor binding without biological activity. The specification goes even further and exemplifies one such analog, *i.e.*, one comprising a deletion of up to 8 amino acids at the N-terminus. Moreover, the specification indicates that such analogs are well known in the art and the reference disclosing such analogs is incorporated by reference in the application. Thus, Applicants do not understand the Examiner's assertion that the term "chemokine analog" is indefinite since the term is defined in the specification as filed and was a known term of art where such analogs had been described previously. Therefore, Applicants respectfully submit that claim 19 is not vague or indefinite in any way and the rejection of this claim under 35 U.S.C. §112, second paragraph, should be reconsidered and withdrawn.

The Examiner asserts that claim 23 lacks at least one active method step and is vague and indefinite. Although Applicants do not necessarily agree with the Examiner, in order to expedite prosecution of the application, Applicants have amended claim 23 to include an active method step, wherein the method comprises "phenotypically knocking out an HIV co-

receptor." This amendment is amply supported by the specification as filed, which provides extensive teachings and reduction to practice of such methods of inhibiting HIV infection, including, but not limited to, at pages 16-21. Thus, this amendment adds no new matter.

The Examiner also asserts that claim 23 is vague and indefinite because it lacks a step that clearly relates back to the preamble. Applicants, while not necessarily agreeing with the Examiner's reasoning, have in a good faith effort to expedite prosecution of this application, amended claim 23 to recite, per the Examiner's suggestion, a phrase relating back to the preamble. More specifically, claim 23, as amended, now recites "wherein said phenotypic knock-out of an HIV co-receptor in said cell inhibits HIV infection of said cell." Support for this amendment is provided throughout the specification as filed no new subject matter has been added by way of this amendment. Applicants respectfully request that the rejection of claim 23 be reconsidered and withdrawn as the claim as amended is not indefinite in any way.

Claim 24 stands rejected because in the Examiner's view there is insufficient antecedent basis for use of the word "the" with respect to each of the four claimed receptors, *i.e.*, C-C chemokine 5 receptor, C-C chemokine 3 receptor, C-C chemokine 1 receptor, and CXR4 receptor. While not necessarily agreeing with the Examiner, in order to expedite prosecution of this application, Applicants have amended the claim by replacing "the" with "a" at each instance. No new matter has been added by way of this amendment, which Applicants respectfully submit overcomes this rejection such that it should be reconsidered and withdrawn.

Claim 28 stands rejected as being vague and indefinite for reciting "the receptor" and for reciting "an analog of a CC or CXC chemokine." Applicants respectfully submit that the cancellation of claim 28 herein has rendered this rejection moot.

Claim 35 stands rejected since, in the Examiner's view, the wherein clause on page 57, lines 1-3, renders the claim unclear as to whether it claims an expression vector or a method of using the vector. While not necessarily agreeing with the Examiner's reasoning, Applicants have amended claim 35 in a good faith effort to expedite prosecution of this application. More particularly, claim 35 now recites that when the expression vector is administered to certain cells the cells exhibit phenotypic knock out of an HIV coreceptor. This amendment is amply supported by the specification as filed, commencing on page 2, line 30, disclosing an expression vector that can mediate phenotypic knock out of, *inter alia*, a chemokine receptor. Thus, this amendment adds no new matter. Additionally, Applicants

respectfully submit that claim 35, as amended, clearly recites an expression vector and not a method of using such vector, and the rejection of this claim under 35 U.S.C. §112, second paragraph, should be reconsidered and withdrawn.

Claim 38 stands rejected as being indefinite in that, in the Examiner's opinion, it is unclear whether the claim recites an expression vector which happens to be in a pharmaceutically acceptable solution or a composition comprising an expression vector and a pharmaceutically acceptable solution. While not necessarily agreeing with the Examiner's position, Applicants, in a good faith effort to expedite the prosecution of this application, have amended claim 38 to recite a composition comprising the vector of claim 35 and a pharmaceutically acceptable solution. Applicants respectfully submit that claim 38, as amended, is not indefinite in any way and that this rejection should be reconsidered and withdrawn.

Claim 39 stands rejected as being vague and indefinite because, in the Examiner's opinion it lacks a step which clearly relates back to the preamble. Although not necessarily agreeing with the Examiner, Applicants have amended claim 39 in a good faith effort to expedite prosecution of this application. That is, the phrase "thereby increasing white blood cell count in said subject with an HIV infection" has been added. This amendment adds no new subject matter, as it is supported by the specification as filed and because it merely relates back to the preamble. Further, Applicants respectfully submit that this amendment overcomes the rejection of claim 39 under 35 U.S.C. §112, second paragraph, and that the rejection should therefore be reconsidered and withdrawn.

In sum, for the reasons set forth previously elsewhere herein, Applicants respectfully submit that claims 8-16, 19, 23-24, 29, and 32-39 (claims 25-28 and 30-32 having been canceled herein) are not indefinite under 35 U.S.C. § 112, second paragraph, and that this rejection should be reconsidered and withdrawn.

Rejection of claims 17, 23, 24, and 32 pursuant to 35 U.S.C. § 102(e)

Claims 17, 23, 24, and 32 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Leavitt et al. (U.S. Patent No. 5,939,538). The Examiner asserts that Leavitt et al. teaches a method of blocking HIV infection by blocking HIV co-receptor RNA expression using ribozymes to cleave HIV co-receptor mRNA, or antisense molecules to bind the mRNA and inhibit translation. In the Examiner's view, the method taught by Leavitt et al. will result in

blocking cell surface expression of the co-receptor. The Examiner also asserts that in Leavitt et al. the target cells for treatment include T cells, macrophages and hematopoietic stem cells. Applicants respectfully submit that Leavitt et al. cannot anticipate claims 17, 23, and 24, as amended, under 35 U.S.C. § 102(e), as more fully set forth below.

Preliminarily, claim 32 has been cancelled herein, thus rendering this rejection moot as to this claim.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, Leavitt must describe each and every element of claims 17, 23, and 24, as amended, in order to anticipate these claims under Section 102(e).

Applicants respectfully submit that Leavitt et al. does not teach each and every element of the claims as now amended. More specifically, Leavitt et al. relates to methods of inhibiting HIV co-receptor protein from being translated, namely cleaving the co-receptor mRNA with a ribozyme or blocking translation of a co-receptor mRNA using an antisense nucleic acid with a sequence that is complementary to the mRNA encoding the co-receptor. However, Leavitt et al. does not teach using an intracellular cytokine, e.g., "intrakine" defined as "any ligand that binds to a C-C chemokine receptor at the cell surface but has been modified to be targeted to the ER of the lymphocyte or other intracellular organelle (specification at page 11, lines 23-25), to bind intracellularly to an HIV co-receptor and prevent its transport to the cell surface, as now recited by claims 17, 23, and claim 24 depending therefrom.

Leavitt has nothing whatsoever to do with retaining receptors intracellularly so they are not expressed on the cell surface using intrakines. Therefore, Leavitt et al. cannot anticipate the present invention in that unlike the Applicants invention, Leavitt et al. provides no guidance as to how to block a co-receptor protein from being transported to the cell surface once it is expressed in the cell. The present application provides methods for inhibiting HIV from binding to co-receptors by blocking co-receptor transport to the surface using intracellular targeted intrakines, which bind to and block co-receptor transport and it provides methods for inhibiting HIV from binding to cell surface co-receptor proteins using secreted chemokines

which compete with HIV and further block it from binding to cell surface co-receptors. Leavitt is completely silent as to these teachings and does not suggest, much less describe, the methods as recited in claims 17, 23, and 24, as amended.

Applicants assert that based on these reasons provided above, Leavitt et al. does not teach each and every element of claims 17, 23, and 24, as amended, and cannot therefore anticipate these claims. Further, claim 32 has been cancelled herein and any rejection of this claim is now moot. For these reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e), based on Leavitt et al., be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each objection and rejection by the Examiner of the specification and claims of the present application has been either overcome or is now inapplicable and that each of remaining claims 1-24, 29, and 33-39 is in condition for allowance. Reconsideration and allowance of each of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

CHEN *ET AL.*

January 17, 2002
(Date)

By: _____

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MARKED UP COPY OF AMENDED SPECIFICATION

Page 3, paragraph at lines 24-27:

"The expression vector of the present invention preferably encodes a chemokine gene product that binds to a C-C chemokine 5 receptor, a C-C chemokine 3 receptor, a C-C chemokine 1 receptor or a CXR4 receptor. Preferred chemokines include, but are not limited to Regulated upon Activation, Normal T cell Expressed, and presumably Secreted (RANTES), Macrophage Inflammatory Protein-1α (MIP-1α), or SDF."

MARKED UP COPY OF AMENDED CLAIMS

8. (Amended) The expression vector of claim 1, wherein said chemokine gene encodes a chemokine that binds to [the] a C-C chemokine 5 receptor, [the] a C-C chemokine 3 receptor, [the] a C-C chemokine 1 receptor or [the] a CXR4 receptor.

9. (Amended) The expression vector of claim 1, wherein said chemokine gene encodes a chemokine that binds to [the] a C-C chemokine 5 receptor.

10. (Amended) The expression vector of claim 1, wherein said [CC] chemokine gene encodes a chemokine that binds to [the] a C-C chemokine 3 receptor.

11. (Amended) The expression vector of claim 1, wherein said [CC] chemokine gene encodes a chemokine that binds to [the] a C-C chemokine 1 receptor.

12. (Amended) The expression vector of claim 1, wherein said [CXC] chemokine gene encodes a chemokine that binds to [the] a CXR4 receptor.

13. (Amended) The expression vector of claim 2, wherein the [encoded] secreted chemokine is RANTES (Regulated upon Activation, Normal T cell Expressed, and presumably Secreted), MIP-1α (Macrophage Inflammatory Protein-1α), or SDF (stromal cell derived factor-1).

14. (Amended) The expression vector of claim 2, wherein said secreted chemokine binds to [the] a chemokine receptor.

15. (Amended) The expression vector of claim 14, wherein one or more amino acids are deleted from the N-terminus of the [encoded] secreted chemokine.

16. (Amended) The expression vector of claim 1, wherein said intracellular retention signal sequence directs [the expressed] a protein expressed from said single intrakine

transcript to the endoplasmic reticulum, Golgi apparatus, a lysosome, an intracellular vesicle or other cellular compartment.

17. (Amended) A method of inhibiting phenotypic expression of a chemokine receptor in a cell, wherein the method comprises blocking cell surface expression of said chemokine receptor by binding of said chemokine receptor with an intrakine.

23. (Amended) A method of inhibiting HIV infection of a cell, [comprising phenotypic knock-out of] said method comprising phenotypically knocking out an HIV co-receptor in said cell by binding of said HIV co-receptor with an intrakine, wherein said phenotypic knock-out of said HIV co-receptor in said cell inhibits infection of said cell.

24. (Amended) The method of claim 23, wherein said co-receptor is [the] a C-C chemokine 5 receptor, [the] a C-C chemokine 3 receptor, [the] a C-C chemokine 1 receptor or [the] a CXR4 receptor.

33. (Amended) The method of claim 29, wherein said CC receptor is [the] a C-C chemokine 5 receptor (CCR5), a C-C chemokine 3 receptor (CCR3), or a C-C chemokine 1 receptor (CCR1).

35. (Amended) [A] An expression vector for treatment of an HIV infection in a subject, wherein said expression vector includes:

an expression region which comprises:

a promoter;

an intracellular retention signal sequence encoding region; and

a chemokine encoding gene;

wherein said intracellular retention signal sequence and said chemokine encoding gene are expressed as a single intrakine transcript from said promoter; and

wherein when said expression vector is administered to lymphocytes, monocytes, macrophages or stem cells of said subject [and wherein] said cells exhibit a phenotypic knock out of an HIV co-receptor.

38. (Amended) [The] A composition comprising the expression vector of claim 35 [, contained in] and a pharmaceutically acceptable solution.

39. (Amended) A method of increasing white blood cell count in a subject with an HIV infection comprising administering to said subject a pharmaceutical composition comprising lymphocytes, monocytes, macrophages or stem cells transduced with a vector of claim 1, thereby increasing white blood cell count in said subject with an HIV infection.